UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF RESEARCH AND DEVELOPMENT
National Center for Environmental Assessment
Research Triangle Park, NC 27711

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OFFICE OF
RESEARCH AND DEVELOPMENT

Dr. Philip K. Hopke
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Dear Phil:

It was good to see you and other CASAC PM Review Panel colleagues again at the CASAC public meeting held at our new EPA RTP campus on July 18-19, 2002 for the purpose of reviewing the April 2002 Third External Review Draft (EPA/600/P-99-002a-bC) of our revised EPA document *Air Quality Criteria for Particulate Matter*. We very much appreciate the helpful, constructive comments and advice provided by you and other members of the PM Review Panel with regard to the subject draft PM Air Quality Criteria Document (PM AQCD) and revisions needed in order to bring its review to closure.

As per discussions at that public meeting, my office (NCEA/RTP) has proceeded to work with our colleagues in EPA's Office of Air Quality Planning and Standards (OAQPS) and others to develop (a) plans for how to address newly identified statistical (GAM modeling) issues affecting assessment of PM time-series epidemiology studies in Chapter 8 (Epidemiology) and Chapter 9 (Integrative Synthesis) of the subject PM AQCD; (b) plans to make necessary changes to the draft document to incorporate any resulting reanalyses of GAM-affected epidemiology studies and other newly available research findings (through April 2002); and (c) a projected future review schedule for the revised draft document. These are to be the main topics of discussion for the follow-up teleconference consultation with the CASAC PM Review Panel, scheduled for 11:00 a.m. to 2:00 p.m. on August 28, 2002.

Accordingly, please find attached the following materials for use in the upcoming teleconference consultation.

Attachment A: Policy-Related Priorities for Selecting Studies for Reanalysis from Among Published Particulate Matter (PM) Epidemiology Studies Using General Additive Models (GAM).

Attachment B: Proposed EPA Plan for Facilitating Preparation and Peer-Review of Reanalyses of Published PM Time-Series Epidemiology Studies Using GAM

Attachment C: Projected Schedule for EPA Development of Revised (Fourth) External Review Draft of PM AQCD and CASAC Review.

Should you or other members of the CASAC PM Review Panel need clarification with regard to any of attached materials please do not hesitate to contact me (Phone: 919-541-4173; e-mail: grant.lester@epa.gov). Thank you.

Sincerely,

Lester D. Grant, Ph.D.
Director, NCEA-RTP

Attachment

cc: Robert Flaak
SAB Staff PM Review Panel Members

Attachment A

Policy-Related Priorities for Selecting Studies for Reanalyis from Among Published Particulate Matter (PM) Epidemiology Studies Using Generalized Additive Models (GAM)

Following the discussion of statistical issues related to the use of generalized additive models (GAM) for time-series epidemiology studies at the July 18-19, 2002 Clean Air Scientific Advisory Committee (CASAC) meeting, NCEA/RTP and OAQPS have considered the list of published PM epidemiology studies assessed in the Third Draft PM AQCD that used GAM in their analyses. Based on policy-related considerations, we have identified a group of studies for which reanalysis to address specific statistical analysis issues would be most useful. In selecting this group of studies, emphasis has been placed on studies that would have the greatest potential to influence EPA review of the PM NAAQS. An overall evaluation of the body of evidence is a fundamental part of the PM NAAQS review, but some studies will provide more information than others when making specific recommendations regarding the PM NAAQS. Our list of priority studies is based on consideration of the following factors:

1. Location of study:

Highest priority will be placed on findings of studies conducted in the U.S. and Canada in conducting risk analyses and evaluating the NAAQS. All studies listed below were conducted in the U.S. or Canada.

2. Indicator:

The use of relevant PM measurements is another important factor for prioritization. Within this category, the highest priority is placed on those studies using measurements of both $PM_{2.5}$ and $PM_{10\text{-}2.5}$. Priority is also placed on those studies using $PM_{2.5,}$ without $PM_{10\text{-}2.5,}$ measurements. In addition, priority is placed on some studies using PM_{10} measurements, where the study focuses on an issue of particular interest.

3. Type of Study:

In considering type of analysis, multi-city studies (U.S. and Canadian) are considered to be of high priority and relevance to the PM NAAQS review. Also, priority is placed on single-city studies that provide information related to specific issues of interest, including the effects of PM and co-pollutants, effects of PM components or use of factor analysis methods, distributed lag analyses, the use of health endpoints other than mortality or hospital admissions, and assessment of harvesting and potential threshold levels.

Proposed List of Policy-Related Priority Studies Drawn from Published U.S. and Canadian PM Epidemiology Studies Using GAM (multi-city studies indicated with ✶)

Studies including both $PM_{2.5}$ and $PM_{10-2.5}$ measurements:

- Burnett, R. T.; Smith-Doiron, M.; Stieb, D.; Cakmak, S.; Brook, J. R. (1999) Effects of particulate and gaseous air pollution on cardiorespiratory hospitalizations. Arch. Environ. Health 54:130-139.
- ✶Burnett, R. T.; Brook, J.; Dann, T.; Delocla, C.; Philips, O.; Cakmak, S.; Vincent, R.; Goldberg, M. S.; Krewski, D. (2000) Association between particulate- and gas-phase components of urban air pollution and daily mortality in eight Canadian cities. Inhalation Toxicol. 12(suppl. 4): 15-39.
- Fairley, D. (1999) Daily mortality and air pollution in Santa Clara County, California: 1989-1996. Environ. Health Perspect. 107:637-641.
- Gold, D. R.; Litonjua, A.; Schwartz, J.; Lovett, E.; Larson, A.; Nearing, L.; Allen, G.; Verrier, M.; Cherry, R.; Verrier, R. (2000) Ambient pollution and heart rate variability. Circulation 101:1267-1273.
- Lin, M.; Chen, Y.; Burnett, R. T.; Villeneuve, P. J.; Krewski, K. (2002) The influence of ambient coarse particulate matter on asthma hospitalization in children: case-crossover and time-series analyses. Environ. Health Perspect. 110:575-581.
- Mar, T. F.; Norris, G. A.; Koenig, J. Q.; Larson, T. V. (2000) Associations between air pollution and mortality in Phoenix, 1995-1997. Environ. Health Perspect. 108:347-353.
- Ostro, B. D.; Broadwin, R.; Lipsett, M. J. (2000) Coarse and fine particles and daily mortality in the Coachella Valley, CA: a follow-up study. J. Exposure Anal. Environ. Epidemiol. 10:412-419.
- ✶Schwartz, J.; Dockery, D. W.; Neas, L. M. (1996) Is daily mortality associated specifically with fine particles? J. Air Waste Manage. Assoc. 46:927-939.
- ✶Schwartz, J.; Neas, L. M. (2000) Fine particles are more strongly associated than coarse particles with acute respiratory health effects in schoolchildren. Epidemiology 11:6-10.
- Sheppard, L.; Levy, D.; Norris, G.; Larson, T. V.; Koenig, J. Q. (1999) Effects of ambient air pollution on nonelderly asthma hospital admissions in Seattle, Washington, 1987-1994. Epidemiology 10: 23-30.

Studies including $PM_{2.5}$ but not $PM_{10-2.5}$ measurements:

- Laden, F.; Neas, L. M.; Dockery, D. W.; Schwartz, J. (2000) Association of fine particulate matter from different sources with daily mortality in six U.S. cities. Environ. Health Perspect. 108:941-947.
- Moolgavkar, S. H. (2000a) Air pollution and mortality in three U.S. counties. Environ. Health Perspect. 108:777-784.

- Moolgavkar, S. H. (2000b) Air pollution and hospital admissions for diseases of the circulatory system in three U.S. metropolitan areas. J. Air Waste Manage. Assoc. 50:271-280.
- Moolgavkar, S. H. (2000c) Air pollution and hospital admissions for chronic obstructive pulmonary disease in three metropolitan areas of the United States. Inhalation Toxicol. 12(Suppl. 4):75-90
- Norris, G.; Young-Pong, S. N.; Koenig, J. Q.; Larson, T. V.; Sheppard, L.; Stout, J. W. (1999) An association between fine particles and asthma emergency department visits for children in Seattle. Environ. Health Perspect. 107: 489-493.
- Stieb, D. M.; Beveridge, R. C.; Brook, J. R.; Smith-Doiron, M.; Burnett, R. T.; Dales, R. E.; Beaulieu, S.; Judek, S.; Mamedov, A. (2000) Air pollution, aeroallergens and cardiorespiratory emergency department visits in Saint John, Canada. J. Exposure Anal. Environ. Epidemiol.: 10: 461-477.

Studies including only PM_{10} measurements:

- ✶Braga, A. L. F.; Zanobetti, A.; Schwartz, J. (2001) The lag structure between particulate air pollution and respiratory and cardiovascular deaths in ten U.S. cities. J. Occup Environ. Med. 43:927-933.
- ✶Janssen, H. A. J.; Schwartz, J.; Zanobetti, A.; Suh, H. H. (2002) Air conditioning and source-specific particles as modifiers of the effect of PM_{10} on hospital admissions for heart and lung disease. Environ. Health Perspect. 110:43-49.
- ✶Schwartz, J. (1999) Air pollution and hospital admissions for heart disease in eight U.S. counties. Epidemiology 10: 17-22.
- ✶Schwartz, J. (2000a) Assessing confounding, effect modification, and thresholds in the association between ambient particles and daily deaths. Environ. Health Perspect. 108:563-568.
- ✶Zanobetti, A.; Schwartz, J.; Dockery, D. W. (2000) Airborne particles are a risk factor for hospital admissions for heart and lung disease. Environ. Health Perspect. 108:1071-1077.

Health Effects Institute (HEI) funded studies: Based on discussions at the CASAC meeting, it is our understanding that HEI is providing funding for reanalysis of recent epidemiology studies funded originally by HEI. Based on the criteria listed above, we also would include the following studies on a priority list for reanalysis.

- ✶Samet, J. M.; Zeger, S. L.; Domenici, F.; Curriero, F.; Coursac, I.; Dockery, D.W.; Schwartz, J.; Zanobetti, A. (2000a,b) The national morbidity, mortality, and air pollution study. Part I: methods and methodologic issues. Part II: morbidity, mortality, and air pollution in the United States. Cambridge, MA: Health Effects Institute: research report no. 94. *Included in this report are sections or appendices that were subsequently published as the following papers*:

- Zeger, S. L.; Thomas, D.; Dominici, F.; Samet, J. M.; Schwartz, J.; Dockery, D.; Cohen, A. (2000) Exposure measurement error in time-series studies of air pollution: concepts and consequences. Environ. Health Perspect. 108: 419-426. (Part I, Section 1)
- Dominici, F.; Zeger, S. L.; Samet, J. (2000) A measurement error model for time-series studies of air pollution and mortality. Biostatistics 1: 157-175. (Part I, Section 2)
- Zeger, S. L.; Dominici, F.; Samet, J. (1999) Harvesting-resistant estimates of air pollution effects on mortality. Epidemiology 10:171-175. (Part I, Section 3)
- Schwartz, J. (2000c) Harvesting and long term exposure effects in the relation between air pollution and mortality. Am. J. Epidemiol. 151:440-448. (Part I, Section 4)
- Schwartz, J. (2000b) The distributed lag between air pollution and daily deaths. Epidemiology 11:320-326. (Part II, Appendix B)

- Goldberg, M. S.; Bailar, J. C., III; Burnett, R. T.; Brook, J. R.; Tamblyn, R.; Bonvalot, Y.; Ernst, P.; Flegel, K. M.; Singh, R. K.; Valois, M.-F. (2000) Identifying subgroups of the general population that may be susceptible to short-term increases in particulate air pollution: a time-series study in Montreal, Quebec. Cambridge, MA: Health Effects Institute; research report 97.
- Lippmann, M.; Ito, K.; Nadas, A.; Burnett, R. T. (2000) Association of particulate matter components with daily mortality and morbidity in urban populations. Cambridge, MA: Health Effects Institute; research report 95.

Attachment B

Proposed EPA Plan for Facilitating Preparation and Peer-Review of Reanalyses of Published PM Time-Series Epidemiology Studies Using GAM

Background: Numerous published PM time-series epidemiology studies assessed in the April 2002 Third External Review Draft of the EPA PM Air Quality Criteria Document (PM AQCD) utilized General Additive Models (GAM) in generating salient results reported in peer-reviewed journal articles and/or other peer-reviewed reports (e.g., HEI Reports). Two major types of statistical issues have been identified as being associated with use of GAM methods in time-series analyses of short-term PM exposure effects: (a) misestimation (i.e., most usually overestimation) of PM effect sizes associated with use of default "convergence criteria" for termination of iterative model backfitting subroutines in S plus software; and (b) "variance estimation" problems (i.e., underestimation of standard errors and confidence intervals impacting associated statistical significance levels), encountered with various software packages (e.g., S plus, SAS, STRATA, etc.). The specific nature and extent of impacts of the above GAM-related problems on quantitative PM effect-size estimates and associated statistical significance determinations can vary widely from study to study, depending on a number of factors, such as: (a) numbers of observations (days of air pollution measurements; numbers of deaths, hospital admissions, etc.); (b) numbers of variables included in the model (e.g., temperature and/or other weather variables; different co-pollutants; spatial and temporal trends, etc); (c) specific approaches to modeling such variables (e.g., use of LOESS smoothing, natural splines, B-splines, etc.), (d) degrees of freedom (d.f.) allocations, and (e) use of sufficiently powerful computing capacities.

Objective. As per discussions at the July 18-19, 2002 CASAC PM Review meeting, it would be useful to accomplish timely Reanalyses (and their peer review) of those published PM time-series studies using GAM approaches assessed in the PM AQCD that are likely to be important in informing PM NAAQS decisions derived as an outcome of the currently ongoing PM NAAQS Review.

Approach. EPA's basic position is that (a) it is the responsibility of the individual investigators who authored the original published PM time-series studies using GAM approaches to carry out and publish the results of reanalyses to address statistical issues of the types noted above; and (b) any funding to be provided for conduct of such reanalyses is most appropriately the responsibility of those agencies or institutions that originally sponsored/funded the published studies. Still, EPA is interested in trying to encourage and facilitate (a) reanalyses of those GAM-related PM studies listed in Attachment A as having a high potential to inform NAAQS decisions, and (b) the peer-review of written reports on such reanalyses in time for consideration in the next (Fourth) draft of the PM AQCD. As described at the July 18-19, 2002 CASAC Meeting, HEI has already taken steps to accomplish expeditious reanalysis of those studies sponsored by them, with the goal of having those reanalyses and written descriptions of them completed in time for review by an HEI peer-review panel in October/November 2002 and

leading to issuance of an HEI report on the reanalyses by January 2003. To encourage/ facilitate timely reanalyses of other high-priority non-HEI sponsored studies identified in Attachment A, EPA proposes to take the following steps:

1. Contact the investigators who authored non-HEI sponsored studies identified in Attachment A to be sure they are aware of the newly surfaced GAM-related statistical issues and to request that they undertake reanalyses of their studies, including more stringent GAM approaches to lessen problems of the type noted above and other alternative modeling (e.g., GLM) approaches and sensitivity analyses, taking into account information and guidance provided by EPA based on recent CASAC discussions and interactions with HEI peer-review panel.

2. Organize and conduct in late September/early October 2002 an EPA-sponsored public workshop to bring together: (a) the investigators conducting reanalyses of HEI-sponsored or other studies listed in Attachment A; (b) some other invited statistical and epidemiological experts; and (c) analogous EPA experts and other pertinent EPA staff engaged in PM related scientific assessment and PM standards review efforts. The workshop is to provide an open forum for reporting out and discussing progress in carrying out reanalyses to date, as well as to allow for post-workshop "mid-course" modifications of approaches before the investigators provide concise written descriptions of their reanalyses (as workshop deliverables) to be submitted for their expeditious peer review.

3. Coordinate with HEI to accomplish timely submittal of the above "reanalyses papers" for peer review by the HEI panel, along with their review of the reanalyses of HEI-sponsored studies. The final product is to be an HEI Report incorporating the "reanalyses papers" and HEI review panel commentary for both HEI-sponsored and non-HEI sponsored reanalyses of Attachment A studies (by January 31, 2003).

In parallel with the above steps, EPA will proceed with the incorporation of revisions to draft PM AQCD materials to reflect public comments and CASAC review of the Third External Review Draft. Revisions will take into account those studies deemed pertinent for PM criteria development published through April 30, 2002 and the results of the above epidemiology reanalyses incorporated in the January HEI Report. Consideration will also be given to any reanalyses of important (e.g., Attachment A) GAM-related time-series studies carried out and/or peer-reviewed under other acceptable auspices, e.g., publication in journals of peer-reviewed short communications describing reanalyses by original investigators, that become available in time for incorporation into the Fourth External Review Draft. With exception of inclusion of such peer-reviewed reanalyses of PM time-series epidemiology analyses originally published before April 30, 2002, EPA does not contemplate inclusion in the Fourth External Review Draft of papers published or accepted for publication beyond the April 30, 2002 date, unless extremely important new information provided by such papers would be likely to have a major impact on PM NAAQS decision making.

Attachment C

Projected Schedule for EPA Development of Revised (Fourth) External Review Draft of PM AQCD and CASAC Review

EPA-sponsored Statistical Issues Workshop	Sept/Oct 2002
HEI Panel Peer Review of Reanalyses of both HEI and non-HEI Sponsored Studies	Nov/Dec 2002
HEI Report on Reanalyses and Review Commentaries	January 2003
Revised (Fourth) External Review Draft *PM AQCD Released for Public Comment/CASAC Review	March 2003
CASAC PM Panel Review of Fourth Draft CD	June 2003
Final PM AQCD Completed	October 2003

* Revised draft to include revisions made in other chapters in parallel to above steps leading to incorporation of time-series epidemiology reanalyses results into Chapters 8 and 9 in February 2003 timeframe.